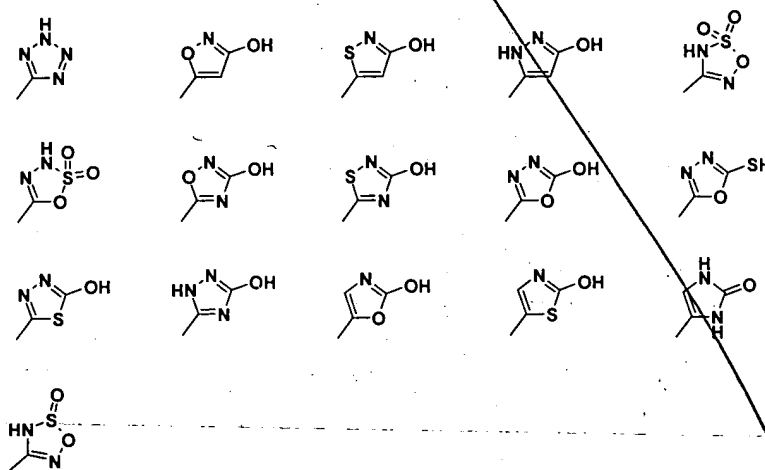


CLAIMS

1. A method of inhibiting at least one intracellular or membrane-associated PTPase that has aspartic acid (Asp) in position 48 using the numbering for PTP1B, the method comprising exposing the PTPase to an inhibitor compound which fits spatially into the active site and the vicinity thereof, said compound comprising the following features and moieties:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and a hydrogen bond with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 wherein the distance between the centroid of said carboxylic acid or carboxylic acid

isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

- IN. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of features IV through V:
- IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and
- V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and
- one or more of the following features VI-XXXVII:
- VI. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and
- VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid

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group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

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VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

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IX. a hydrophilic group that forms a hydrogen bond or forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

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X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 is 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

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XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

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XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of

Dr. A. J. C. King

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said hydrophilic group and the amide nitrogen group of said arginine 47 is 2 ranges from 7-4.0 Å;

- 5 XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;
- 10 XIV. a hydrophilic group that interacts with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;
- 15 XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 20 XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 25 XVII. a hydrophobic group that reaches a proximity interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;
- 30 XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the

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distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

- 5 XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;
- 10 XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;
- 15 XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;
- 20 XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;
- 25 XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;
- 30 XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and

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the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

5 XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

10 XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

15 XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

20 XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

25 XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

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XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

XXXV. a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

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XXXVI: a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII: a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and (i) the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, (ii) the centroid of said glycine 259 ranges from 4.7-7.7 Å, and (iii) the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

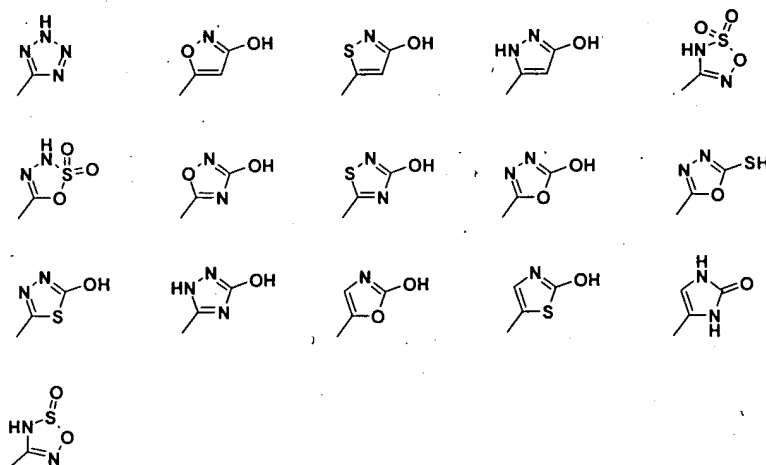
2. A method for inhibiting at least one intracellular or membrane-associated PTPase that has an aspartic acid (Asp) at position 48 using the numbering for PTP1B, the method comprising exposing the PTPase to an inhibitor compound which fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

I. an oxalamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

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wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid group or carboxylic acid isostere group and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and
at least one of the following features IV through V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and
one or more of the following features VI through XXXVII:

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- 5 VI. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and
- 10 VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and
- 15
- 20 VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;
- 25
- IX. a hydrophilic group that forms a hydrogen bond or forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;
- 30
- X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and

the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

5 XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

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XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

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XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

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XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;

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XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

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- 5 XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 10 XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;
- 15 XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;
- 20 XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;
- 25 XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;
- 30 XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

- 5 XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;
- 10 XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;
- 15 XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;
- 20 XXV. a hydrophilic group that forms a hydrogen bond with one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 is 2.7-4.0 Å;
- 25 XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;
- 30 XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the

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guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

5 XXVIII.a hydrophilic group that forms a salt bridge with the
guanidinium group of arginine 254 such that the distance
between the centroid of said hydrophilic group and the
centroid of the guanidinium group of said arginine 254 ranges
from 2.7-4.0 Å;

10 XXIX.a hydrophobic group that interacts with the side chain
methylene groups of arginine 254 such that the distance
between the centroid of said hydrophilic group and the
centroid of the methylene groups of said arginine 254 ranges
from 4.4-5.1 Å;

15 XXX.a hydrophilic group that forms a hydrogen bond with one or
more hydrogen atoms donated by the guanidinium group of
arginine 24 such that the distance between the centroid of
said hydrophilic group and the centroid of the guanidinium
20 group of said arginine 24 ranges from 2.7-4.0 Å;

25 XXXI.a hydrophilic group that forms a salt bridge with the
guanidinium group of arginine 24 such that the distance
between the centroid of said hydrophilic group and the
centroid of the guanidinium group of said arginine 24 ranges
from 2.7-4.0 Å;

30 XXXII.a hydrophobic group that interacts with the side chain
methylene groups of arginine 24 such that the distance
between the centroid of said hydrophilic group and the
centroid of the methylene groups of said arginine 24 is 4.4-5.1
Å;

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XXXIII.a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

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XXXIV.a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

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XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

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XXXVI.a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

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XXXVII.a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å.

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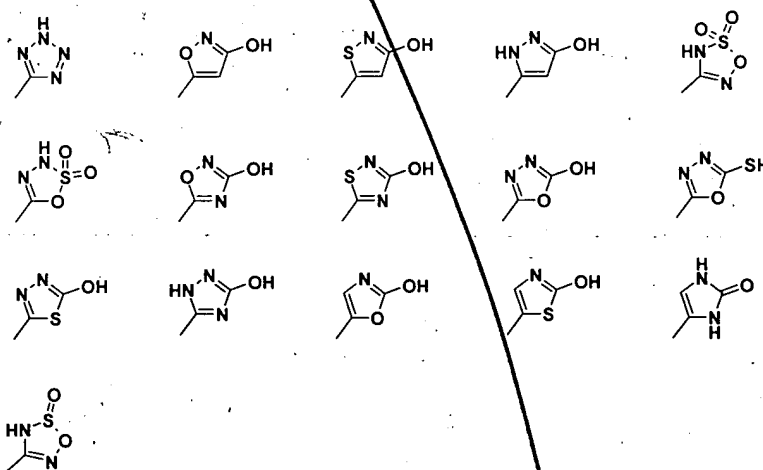
30 3. A method of inhibiting at least one PTPase selected from the group consisting of PTP1B, TC-PTP and other PTPase that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

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- I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

- II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or acid isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

- III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and one or more of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

one or more of the following features VI through XXXVII:

VI. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å; and

VII. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the

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centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a salt bridge with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;

XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;

XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

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- 5 XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;
- 10 XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 15 XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 20 XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;
- 25 XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;
- 30 XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

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5 XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

10 XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

15 XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

20 XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

25 XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

30 XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

5 XXVI.a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

10 XXVII.a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

15 XXVIII.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

20 XXIX.a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

25 XXX.a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

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XXXI.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the

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centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

5 XXXII.a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

10 XXXIII.a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

15 XXXIV.a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

20 XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

25 XXXVI.a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

30 XXXVII.a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said

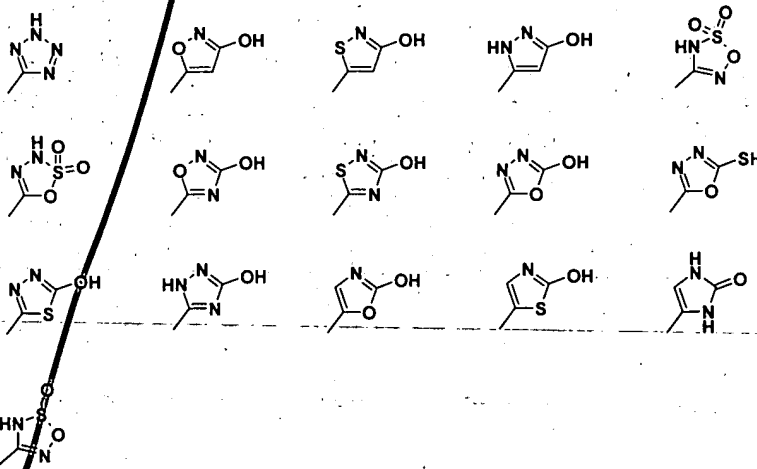
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methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

4. A method of inhibiting at least one PTPase selected from the group consisting of PTP1B, TC-PTP and other PTPase that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

- I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (i) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (ii) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and
- II. (a) a carboxylic acid group or (b) carboxylic acid isostere group selected from the following 5-membered heterocycles



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and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

- VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;
- IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;
- X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;
- XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;
- XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of

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arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;

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- XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;
- 10
- XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;
- 15
- XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 20
- XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
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- XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;
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XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the

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distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

5 XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

10 XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

15 XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

20 XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

25 XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

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5 XXX.a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

10 XXXI.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

15 XXXII.a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

20 XXXIII.a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;

25 XXXIV.a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;

30 XXXV.a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;

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XXXVI. a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

XXXVII. a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

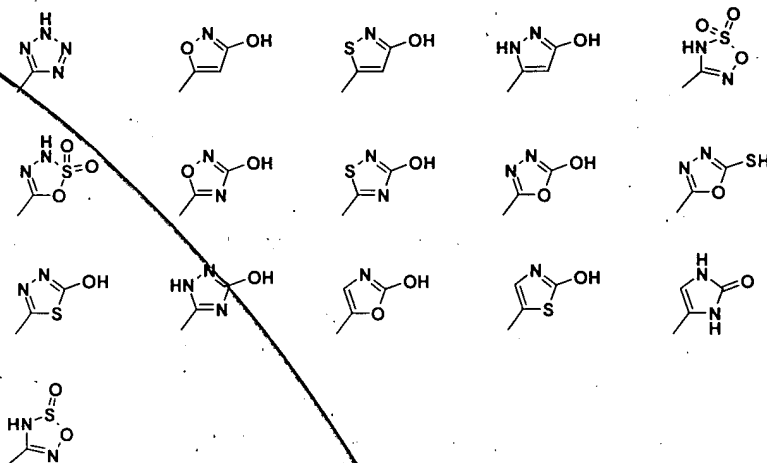
5. A method of inhibiting a PTPase selected from the group consisting of PTP1B, TC-PTP and other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

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wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the following features IV and V:

IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 3.55-5.1 Å; and/or

V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 is 4.4-6.5 Å; and one or more of the following features VI-XXXVII

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VI. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å;

VII. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 is 3.4-4.1 Å;

VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;

IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;

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- X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;
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- XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;
- 15
- XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;
- 20
- XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;
- 25
- XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;
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- XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of

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said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

5 XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

10 XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

15 XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;

20 XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

25 XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

30 XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between

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the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

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XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

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XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

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XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

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XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

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XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

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XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium

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group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

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XXVIII.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

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XXIX.a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

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XXX.a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

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XXXI.a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

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XXXII.a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;

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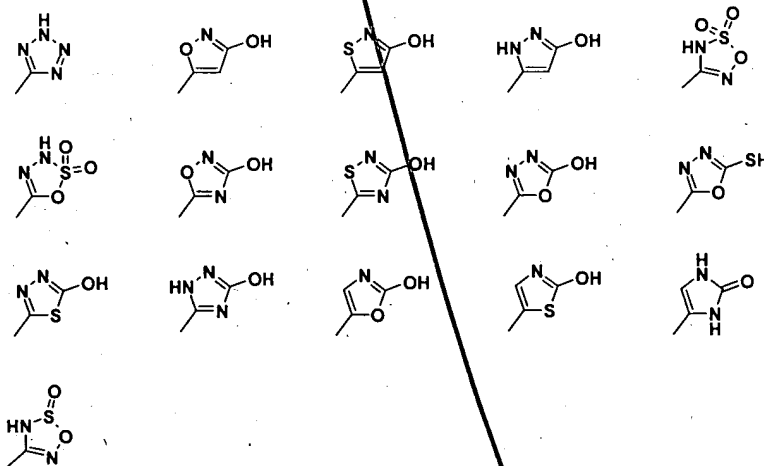
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spatially into the active site of said PTPase and the vicinity thereof, said compound comprising the following features and moieties:

- I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

- II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or said isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said Lysine 120 ranges from 3.4-4.1 Å; and

- III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of

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said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the following features IV and V

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IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; and

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V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and at least one of the following features VI through XXXVII:

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VI. two oxygen atoms which form hydrogen bonds via a water molecule to the side chain carboxylic acid group of aspartic acid 48 such that the distance between each of the two oxygen atoms and the centroid of said water molecule ranges from 2.5-3.6 Å and that the distance between said water molecule and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 2.5-3.6 Å and that the distance between said two oxygen atoms ranges from 2.5-3.0 Å; and

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VII. an amino group which forms a salt bridge to the side chain carboxylic acid group of aspartic acid 48 such that the distance between the nitrogen atom of said amino group and the centroid of said side chain carboxylic acid group of aspartic acid 48 ranges from 3.4-4.1 Å;

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- 5 VIII. a hydrophobic group that interacts with the side chain methylene groups of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the methylene groups of said tyrosine 46 ranges from 4.4-5.1 Å;
- 10 IX. a hydrophilic group that forms a hydrogen bond with aspartic acid 181 such that the distance between the centroid of said hydrophilic group and the centroid of the carboxylic acid of said aspartic acid 181 ranges from 4.4-5.1 Å;
- 15 X. a hydrophobic group that interacts with tyrosine 46 and the methylene side chain atoms of arginine 47 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.7-5.2 Å and the centroid of the methylene side chain atoms of said arginine 47 ranges from 4.5-5.5 Å;
- 20 XI. a hydrophilic group that forms a hydrogen bond with the one or more hydrogen atoms donated by the guanidinium group of arginine 47 such that the distance between the centroid of said hydrophilic group and the guanidinium group of said arginine 47 ranges from 2.7-3.5 Å;
- 25 XII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of arginine 47 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said arginine 47 ranges from 2.7-4.0 Å;
- 30 XIII. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between the centroid

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of said hydrophilic group and the amide nitrogen group of said aspartic acid 48 ranges from 2.7-4.0 Å;

- 5 XIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of asparagine 44 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said asparagine 44 ranges from 2.7-4.0 Å;
- 10 XV. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 15 XVI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 20 XVII. a hydrophobic group that interacts with the side chain methylene groups of arginine 45 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;
- 25 XVIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of arginine 45 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said arginine 45 ranges from 2.7-4.0 Å;
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XIX. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of tyrosine 46 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said tyrosine 46 ranges from 2.7-4.0 Å;

XX. a hydrophilic group that forms a hydrogen bond with the side chain amino group of lysine 41 such that the distance between the centroid of said hydrophilic group and the amino group of said lysine 41 ranges from 2.7-4.0 Å;

XXI. a hydrophobic group that interacts with the side chain methylene groups of lysine 41 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said lysine 41 ranges from 4.4-5.1 Å;

XXII. a hydrophobic group that interacts with the side chain methylene groups of leucine 88 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said leucine 8 ranges from 4.4-5.1 Å;

XXIII. a hydrophilic group that forms a hydrogen bond with the side chain hydroxy group of serine 118 such that the distance between the centroid of said hydrophilic group and the hydroxy group of said serine 118 ranges from 2.7-4.0 Å;

XXIV. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of leucine 119 such that the distance between the centroid of said hydrophilic group and the amide carbonyl group of said leucine 119 ranges from 2.7-4.0 Å;

XXV. a hydrophilic group that forms a hydrogen bond with the one of the hydrogen atoms donated by the side chain amide

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nitrogen of glutamine 262 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glutamine 262 ranges from 2.7-4.0 Å;

5 XXVI. a hydrophilic group that forms a hydrogen bond with the hydrogen atom donated by the backbone amide group nitrogen of glycine 259 such that the distance between the centroid of said hydrophilic group and the amide nitrogen group of said glycine 259 ranges from 2.7-4.0 Å;

10 XXVII. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the side chain guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

15 XXVIII. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 254 ranges from 2.7-4.0 Å;

20 XXIX. a hydrophobic group that interacts with the side chain methylene groups of arginine 254 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 254 ranges from 4.4-5.1 Å;

25 XXX. a hydrophilic group that forms a hydrogen bond with one or more hydrogen atoms donated by the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;

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- 5 XXXI. a hydrophilic group that forms a salt bridge with the guanidinium group of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the guanidinium group of said arginine 24 ranges from 2.7-4.0 Å;
- 10 XXXII. a hydrophobic group that interacts with the side chain methylene groups of arginine 24 such that the distance between the centroid of said hydrophilic group and the centroid of the methylene groups of said arginine 24 ranges from 4.4-5.1 Å;
- 15 XXXIII. a hydrophilic group that forms a hydrogen bond with the backbone amide carbonyl group of aspartic acid 48 such that the distance between the centroid of said hydrophilic group and the backbone amide carbonyl group of said aspartic acid 48 ranges from 2.7-3.5 Å;
- 20 XXXIV. a hydrophobic group that interacts with the side chain atoms of methionine 258 such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.5-6.2 Å;
- 25 XXXV. a hydrophobic group that interacts with glycine 259 such that the distance between the centroid of said hydrophobic group and the centroid of the alpha-carbon atom of said glycine 259 ranges from 4.5-6.2 Å;
- 30 XXXVI. a hydrophobic group that interacts with phenylalanine 52 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic group of said phenylalanine 52 ranges from 4.1-9.1 Å; or

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XXXVII. a hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket such that the distance between the centroid of said hydrophobic group and the centroid of the side chain of said methionine 258 ranges from 4.1-7.2 Å, the centroid of said glycine 259 ranges from 4.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å;

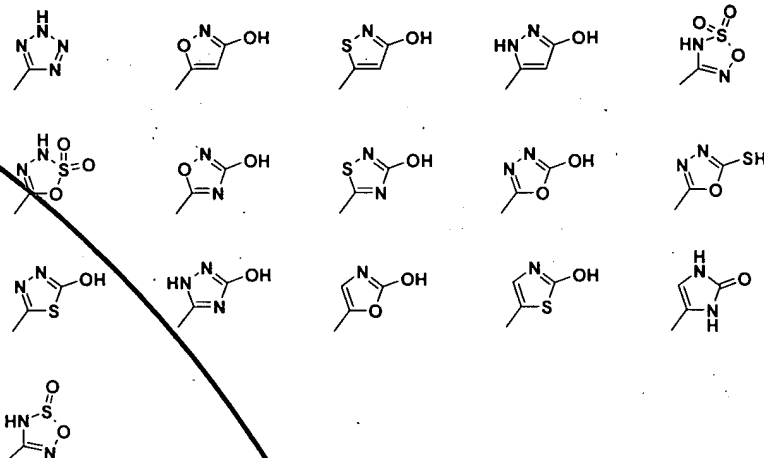
7. A method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B) and/or T-Cell Protein Tyrosine Phosphatase which (TC-PTP) and/or other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising:

I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and forms a hydrogen bond with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

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wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

- III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the following features IV and V:
- IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or
- V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å.

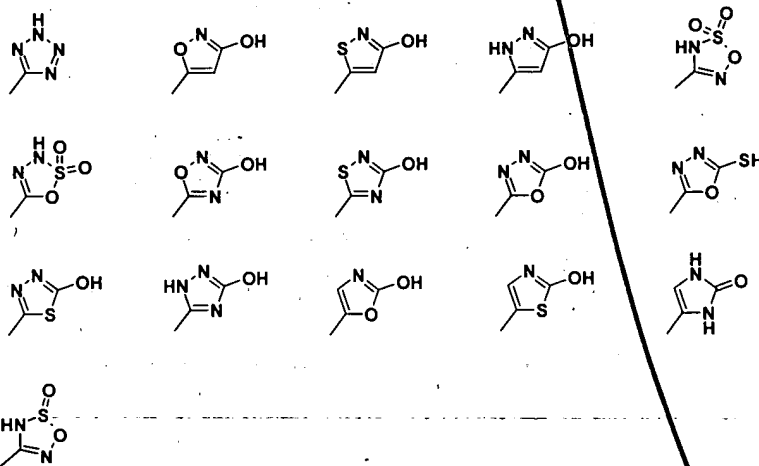
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8. A method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B), T-Cell Protein Tyrosine Phosphatase and other PTPases that are structurally similar to PTP1B comprising exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising:

- I. an oxalylamide which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the carboxylic acid group of said oxalylamide group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å, (II) said arginine 221 amide nitrogen ranges from 3.5-4.2 Å and the distance between the amide carbonyl group of said oxalylamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

- II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance

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between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

- 5 III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 wherein the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and at least one of the features IV and V:
- 10 IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å;
- 15 or
- 20 V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å;

9. A method of inhibiting at least one PTPase selected from the group consisting of Protein Tyrosine Phosphatase 1B (PTP1B), T-Cell Protein Tyrosine Phosphatase (TC-PTP) and other PTPases that are

25 structurally similar to PTP1B which comprises exposing said PTPase to a compound that fits spatially into the active site of said PTPase and the vicinity thereof, said compound comprising:

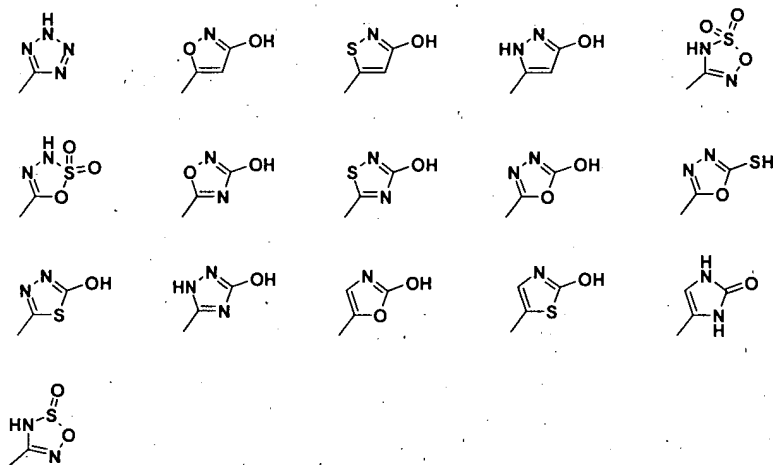
- 30 I. a phosphate isostere which forms a salt bridge to the guanidinium group of arginine 221 and interacts with a hydrogen atom donated by the backbone amide nitrogens of arginine 221 and glycine 220 such that the distance between the centroid of the phosphate isostere group and (I) the centroid of said guanidinium group ranges from 3.50-4.20 Å,

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(II) said arginine 221 backbone amide nitrogen ranges from 3.5-4.2 Å, and (III) said glycine 220 backbone amide nitrogen ranges from 2.7-3.5 Å; and

- 5 II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles



10 wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

- 15 III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

- 20 IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å;
or

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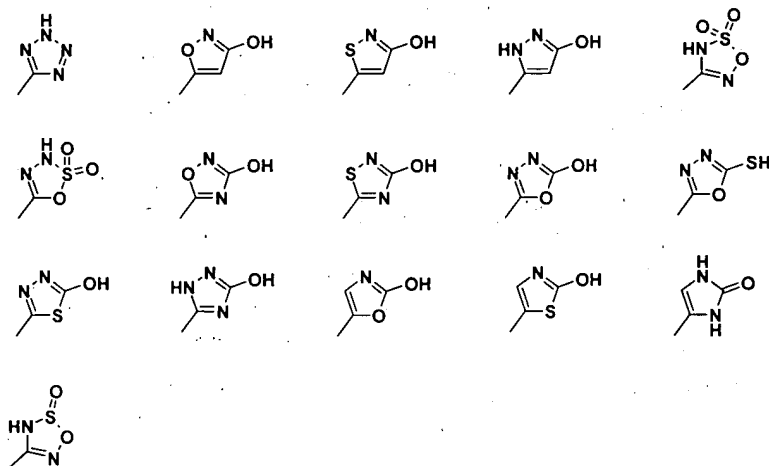
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of said oxalamide group and the said glycine 220 amide nitrogen ranges from 2.7-3.5 Å; and

- II. (a) a carboxylic acid group or (b) a carboxylic acid isostere group selected from the following 5-membered heterocycles

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wherein said acid or isostere group forms a salt bridge to the side chain amino group of lysine 120 such that the distance between the centroid of said carboxylic acid or carboxylic acid isostere and the side chain nitrogen atom of said lysine 120 ranges from 3.4-4.1 Å; and

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- III. a hydrophobic group that interacts with the aromatic ring of tyrosine 46 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said tyrosine 46 ranges from 4.4-5.1 Å; and

15

- IV. a hydrophobic group that interacts with the aromatic ring of phenylalanine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said phenylalanine 182 ranges from 4.4-5.1 Å; or

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- V. a hydrophobic group that interacts with the imidazole ring of histidine 182 such that the distance between the centroid of said hydrophobic group and the centroid of the aromatic ring of said histidine 182 ranges from 4.4-6.5 Å; and

5

wherein the distance between the centroid of the carboxylic acid group of said oxalylamide group and the centroid of (I) said carboxylic acid or carboxylic acid isostere ranges from 4.9-5.9 Å, (II) said amino group ranges from 8.0-14.0 Å and between the centroid of said carboxylic acid or carboxylic acid isostere and said amino group ranges from 4.8-5.8 Å or

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wherein the distance between the centroid of the carboxylic acid group of said oxalylamide group and the centroid of (I) said carboxylic acid or carboxylic acid isostere ranges from 4.9-5.9 Å, (II) said oxygen atoms are ranges from 8.0-14.0 Å and between the centroid of said carboxylic acid or carboxylic acid isostere and said oxygen atoms are ranges from 5.0-7.9 Å.

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11. The method of claim 1 to 6 wherein said hydrophobic group that interacts with the aromatic group of tyrosine 46 and/or the aromatic group of phenylalanine/histidine 182 is an aryl group optionally substituted.

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12. The method of claim 11 wherein said aromatic group that interacts with tyrosine 46 and/or phenylalanine/histidine 182 is phenyl optionally substituted.

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13. The method of claim 11 wherein said aromatic group that interacts with tyrosine 46 and/or phenylalanine/histidine 182 is thiophenyl optionally substituted.

14. The method of claim 12 wherein said phenyl optionally substituted that interacts with tyrosine 46 and/or phenylalanine 182 is naphthyl.
15. The method of claim 13 wherein said thiophenyl optionally substituted that interacts with tyrosine 46 and/or phenylalanine/histidine 182 is thieno[2,3-c]pyridyl optionally substituted.
16. The method of claim 1 to 6 wherein said hydrophobic group that interacts with tyrosine 46 and arginine 47 is an aryl group optionally substituted.
17. The method of claim 16 wherein said aromatic group that interacts with tyrosine 46 and arginine 47 is phenyl optionally substituted.
18. The method of claim 17 wherein said phenyl optionally substituted that interacts with tyrosine 46 and arginine 47 is isoindolyl-1,3-dione optionally substituted of which one of the isoindol carbonyl oxygen atoms interacts with a hydrogen atom donated by the backbone amide nitrogen of aspartic acid 48 such that the distance between these two atoms ranges from 2.7-3.5 Å.
19. The method of claim 18 wherein said isoindolyl-1,3-dione optionally substituted that interacts with tyrosine 46 and arginine 47 is 4-hydroxy-isoindolyl-1,3-dione of which the hydroxy group interacts with a hydrogen atom donated by the backbone amide nitrogen of arginine 47 wherein the distance between the hydroxy group and the amide nitrogen of arginine 47 ranges from 2.7-3.5 Å.
20. The method of claim 1 to 6 wherein said hydrophobic group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket is an aryl group optionally substituted.

21. The method of claim 20 wherein said aryl group that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket is phenyl optionally substituted.

5 22. The method of claim 21 wherein said phenyl optionally substituted that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket is isoindolyl-1,3-dione optionally substituted wherein the distance between the centroid of the phenyl ring of said isoindolyl-1,3-dione and the centroid of the side chain of
10 said methionine 258 ranges from 6.1-7.2 Å, the centroid of said glycine 259 ranges from 6.7-7.7 Å, and the centroid of the side chain of said phenylalanine 52 ranges from 4.1-9.1 Å.

15 23. The method of claim 22 wherein said isoindolyl-1,3-dione optionally substituted that interacts with methionine 258, glycine 259 and phenylalanine 52 being part of a hydrophobic pocket is 5-methoxy-isoindolyl-1,3-dione of which the methoxy group interacts with the side chain atoms of methionine 258 wherein the distance between the
20 centroid of said methoxy group and the centroid of the side chain of said methionine 258 ranges from 4.4-5.6 Å.

24. The method of claim 1-6 wherein said hydrophilic group that interacts with the one of the hydrogen atoms donated by the side chain amide
25 nitrogen of glutamine 262 is 1,1-dioxo-1,2-dihydro-1H-benzo[d]isothiazol-3-one.

25. The method of claim 1-6 wherein said hydrophilic group that interacts with the one of the hydrogen atoms donated by the side chain amide
30 nitrogen of glutamine 262 is 2,3-dihydro-benzo[d]isothiazol-1,1-dioxide.

26. The method of claim 1 wherein the compound is selected from the following:

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- 5-(4-Chloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-(2,4-Dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 5 5-(4,5,6,7-Tetrachloro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 10 5-(1,3-Dioxo-1,3-dihydro-benzo[f]isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester methyl ester;
 Oxalic acid (3-carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl) ester;
- 15 7-Hydroxymethyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-(((Benzo[1,3]dioxole-5-carbonyl)-amino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 20 5-(3-Imidazol-1-yl-2,5-dioxo-pyrrolidin-1-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 2-(Oxalyl-amino)-5-phenylcarbamoyl-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 25 2-(Oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3,7-dicarboxylic acid 7-ethyl ester;
 7-Benzylcarbamoyl-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 30 5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyrazin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

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- 7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylloxymethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5 7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(3-(2,4-Dimethoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
2-((3-Carboxy-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-5-ylmethyl)-carbamoyl)-nicotinic acid;
10 5-(4-Fluoro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
15 5-(4-Benzoyloxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(5,7-Dioxo-5,7-dihydro-[1,3]dioxolo[4,5-f]isoindol-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
20 7-(2,4-Dioxo-5-pyridin-2-ylmethylene-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(2,4-Dioxo-5-pyridin-2-ylmethyl-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
25 7-(5-(4-Methoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(5-(4-Acetylamino-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-(5-(3,5-Dimethoxy-benzylidene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
30 7-(5-(1H-Imidazol-4(5)-ylmethylene)-2,4-dioxo-thiazolidin-3-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
7-((2-(4-Methanesulfonyl-phenyl)-acetylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;

- 5-(1,3-Dioxo-4,7-epoxido-1,3,4,5,6,7-hexahydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-((2-Amino-3-phenyl-propionylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 5 7-(((2R)-2-Amino-3-phenyl-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-((2-Acetylamino-3-(4-hydroxy-phenyl)-propionylamino)-methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-((2-Acetylamino-3-methyl-butyrylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 10 5-(5-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(4-Acetylamino-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 15 5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-b]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(5,7-Dioxo-5,7-dihydro-pyrrolo[3,4-c]pyridin-6-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 20 5-(5-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(5-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(4-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 25 5-(4-Nitro-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1H-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 2-(Oxalyl-amino)-7-(3-oxo-3H-benzo[d]isoxazol-2-ylmethyl)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
- 30 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-ethyl ester;
 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

(L)-5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 5 5-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 2-(Oxalyl-amino)-5-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 or a pharmaceutically acceptable salt thereof.

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27. The method of claim 1 wherein the compound is selected from the following:

- 5-(5-Methoxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 15 7-(((Benzo[1,3]dioxole-5-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(4-(4-Chloro-phenylsulfanyl)-6-methyl-1,3-dioxo-1,3-dihydro-pyrrolo[3,4-c]pyridin-2-ylmethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 20 7-(3-(2,4-Dimethoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-((2-(4-Methanesulfonyl-phenyl)acetylamino)methyl)-2-(oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 7-((2-Acetylamino-3-(4-hydroxy-phenyl)propionylamino)methyl)-2-
 25 (oxalyl-amino)-4,7-dihydro-5H-thieno[2,3-c]pyran-3-carboxylic acid;
 5-(S)-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 7-(4-Hydroxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 30 2-(Oxalyl-amino)-5-(S)-(1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
 5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

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- 5-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-methyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5 5-((1,1-Dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 7-((1,1-Dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 10 5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5-(7-Benzoyloxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 15 5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 20 7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 7-(7-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 25 7-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 7-(((5-Benzoyloxy-1*H*-indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 30 7-(((6-Bromo-2-*p*-tolyl-quinoline-4-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

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- 6-(4-Methoxy-benzyl)-7-(((5-methyl-2-phenyl-2*H*-[1,2,3]triazole-4-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 5 7-(((1*H*-Indole-3-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 7-((4-Ethoxy-2-hydroxy-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 10 7-((4-Benzoylamino-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 7-(((Biphenyl-4-carbonyl)-amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 15 7-(((1*H*-Indole-2-carbonyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 7-((3-Biphenyl-4-yl-acryloylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 20 6-(4-Methoxy-benzyl)-7-(((5-methoxy-1*H*-indole-2-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 25 7-((4-Benzyl-benzoylamino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 6-(4-Methoxy-benzyl)-7-(((naphthalene-1-carbonyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 30 6-(4-Methoxy-benzyl)-5-((2-naphthalen-2-yl-ethylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;
- 5-((2-Benzo[1,3]dioxol-5-yl-acetylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-*c*]pyridine-3-carboxylic acid;

- 5-((2-Dibenzofuran-2-yl-ethyl)amino)methyl)-6-(4-methoxy-benzyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5 6-(4-Methoxy-benzyl)-5-((2-(5-methoxy-2-methyl-1*H*-indol-3-yl)-acetyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5-(*R*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 10 5-(*S*)-(7-Methoxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5-(*S*)-(4-Hydroxy-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 2-(*S*)-(Oxalyl-amino)-5-((4-phenoxy-benzylamino)methyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 15 5-(*S*)-((4-Acetyl-amino-benzylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 7-(*S*)-((Acetyl-(4-phenoxy-benzyl)amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 7-(*S*)-((Acetyl-benzyl-amino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 20 5-(*S*)-((1,1-Dioxo-1*H*-benzo[d]isothiazol-3-ylamino)methyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 5-(4-Benzyl-oxy-1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 25 5-(6-Methoxy-4-methoxycarbonyl-1-oxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;
- 2-(Oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3-carboxylic acid;
- 30 2-(Oxalyl-amino)-7-(1,1,3-trioxo-1,3-dihydro-1*H*-benzo[d]isothiazol-2-ylmethyl)-4,7-dihydro-5*H*-thieno[2,3-c]pyridine-3-carboxylic acid;
- 7-(*R*)-Carbamoyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-(2-oxo-tetrahydro-thiophen-3-ylcarbamoyl)-
4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-3-carboxylic acid;

2-(Oxalyl-amino)-5-(S)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

5 2-(Oxalyl-amino)-7-(R)-phenylcarbamoyl-4,5,6,7-tetrahydro-thieno[2,3-
c]pyridine-3-carboxylic acid;

5-(R),7-(R)-Bis-benzyloxymethyl-2-(oxalyl-amino)-4,5,6,7-tetrahydro-
thieno[2,3-c]pyridine-3-carboxylic acid;

6-Benzyl-2-(oxalyl-amino)-5-(1,1,3-trioxo-1,3-dihydro-1,6-
10 benzo[d]isothiazol-2-ylmethyl)-4,5,6,7-tetrahydro-thieno[2,3-c]pyridine-
3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

15 28. The method of claim 1 wherein said compound is of the Formula 1.

29. The method of any one of claims 1 to 10 wherein said exposing
step is effected by administering said compound to a mammal
including a human in need of said inhibition.

20 30. The method of claim 29, wherein said mammal has a disease
selected from the group consisting of autoimmune diseases, acute
and chronic inflammation, osteoporosis, various forms of cancer and
malignant diseases, and type I diabetes, type II diabetes, and obesity.

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Sub
B³

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B⁴